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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	11

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,320	BARRY ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *6, 7, 23, 24, 26, and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8-12, 16, 21, 22, 25, 28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

Election/Restrictions

Applicant's arguments filed 9/03/02 have been fully considered but they are not persuasive. Applicant's election with traverse of Group I, claims 1-12, 16, 21, 22-24, and 25-29 in paper No. 10 is acknowledged. The traversal is first on the ground(s) that the examiner erred in adding recitations to Claim 1. With respect to applicant's argument, the examiner responds by explaining that the method claims are in improper Markush format. See Ex parte Markush, 1925 C.D. 126 and In re Weber, 198 USPQ 334. Claim 1 and those following are improperly joined, as the claimed methods require the detection of distinct target molecules(ie., nucleic acid, antibody). The elements encompassed in the claim are not obvious variants over each other and as a result are considered by the examiner to be improperly joined. It is noted that the applicant's 2nd argument, with respect to linking claims is considered to be convincing and as a result Claims 1-4 will be examined according to the MPEP's guidance of examining the linking claim with the invention elected and providing that "should any linking claim be allowed, the restriction requirement must be withdrawn." In response to applicant's 3rd argument on the grounds that the action incorrectly restricted the individual mutations, the examiner maintains however, that the *Official Gazette* and notices posted on the PTO website have included guidance "to include up to 10 nucleotide sequences per application." The examiner retains his/her discretion in the inclusion of "up to 10 sequences." However, it is further maintained that the examiner adhered to the PTO policy concerning restriction practice as defined in *35 U.S.C. 121*, "if two or more independent and distinct inventions are claimed in one application, the

commissioner may require the application to be restricted to one of the inventions." Furthermore, the searches required to examine each of the instantly claimed polynucleotides would be different, requiring a search of different classes, different electronic databases and the use of different key words in such a search. As such, the restriction is still deemed proper and is therefore made FINAL.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code(See for ex. Pg. 10). See MPEP § 608.01.

Priority

Acknowledgement of the provisional application drawn to this same subject matter has been made. The filing date of the instant claims is deemed to be the filing date of the provisional application 60/214,187 06/26/2000.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-5, 8-12, 16, 21, 22, 25, 28 and 29, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of determining the ability of a *Mycobacterium tuberculosis* bacterium to oxidize a thiocarbonyl found in the drugs ethionamide(ETA), thiacetazone(TA), and thiocarlide(TC), said method comprising detecting a mutation(from the table below *) in an EtaA gene of said bacterium, wherein detection of the mutation(from the table below*) is indicative of decreased ability to oxidize a thiocarbonyl found in the drugs ETA, TA, and TC, does not reasonably provide enablement for methods of determining the ability of a *M. tuberculosis* bacterium to oxidize any thioamide or any thiocarbonyl, said method comprising detecting any mutation in the EtaA gene in said bacterium, wherein detection of the mutation is indicative of decreased ability to oxidize any thioamide or any thiocarbonyl. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

*Table

Nucleotide position of frameshift mutations/ Related Drug(s) with decreased oxidative ability	Amino Acid position of SNP/ Related Drug(s) with decreased oxidative ability
Δ 1 nt 65 / ETA, TA, TC	G43→C / ETA, TA, TC
+ 1 nt 811 / ETA, TA, TC	P51→L / ETA, TA, TC
	D58→A / ETA, TA, TC
	Y84→D / ETA, TA, TC
	T342→K / ETA, TA
	A381→P / ETA, TA, TC

Claims 1-5, 8-12, 16, 21, 22, 25, 28 and 29 are broadly drawn to methods of determining the ability of a *M. tuberculosis* bacterium to oxidize any thioamide or any thiocarbonyl, said method comprising detecting any mutation in the EtaA gene in said bacterium, wherein detection of the mutation is indicative of decreased ability to oxidize any thioamide or any thiocarbonyl. The specification teaches a series of mutations, those listed above in the table, that have been found to be associated with conferring drug resistance, as a result of their inability to oxidize the thiocarbonyl groups, to antituberculosis medication used in patient isolates. The specification further teaches a study involving 3 such thiocarbonyl-containing antituberculosis medications; ETA, TA, and TC. The specification teaches that the mutations, listed in the table, resulted in the bacterium's inability to oxidize the thiocarbonyl within the drug and consequently, the mutations conferred a drug-resistance to the bacterium. The specification also teaches the low

rate at which the *M. tuberculosis*(MTb) bacterium experiences "synonymous" mutations; that is MTb rarely has random mutation that do not affect the gene sufficiently so that the enzyme encoded by the gene has reduced ability to activate a thioamide prodrug(Specification Page 12). The specification teaches in Figure 4C that several strains with mutations were conferred with drug susceptibility instead of resistance.

The specification does not teach that every mutation in the EtaA gene confers a drug-resistance to the bacterium as a result of its inability to oxidize thiocarbonyl groups. The specification also does not teach the way in which each drug, ETA, TA, TC, or INH differs; nor does it teach the characteristic shared between all drugs responsible for conferring the phenotype. The specification does not teach the other mutations in the EtaA gene that would be indicative of either the drug-resistant phenotype, or the drug-sensitive phenotype. The specification further omits any teaching of a common property represented within each mutation that is responsible for the resulting phenotype of drug resistance because of the inability to oxidize the thiocarbonyl groups. Additionally, the specification teaches that each of the drugs, ETA, TA, and TC confer different phenotypes to the bacterium. The specification does not teach how or why such supposedly similar thiocarbonyl-containing antituberculosis medications confer varying degrees, if at all, of drug resistance. As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the

invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, what other mutations may exist in addition to those listed in Figure 4C and additionally which methods could be used predictably to determine the presence of these mutations. Furthermore, one cannot readily anticipate which of the mutations within the gene(i.e. mutations other than those set forth in Table 4C) actually result in the inability to oxidize thiocarbonyl groups and that would be associated with a patient that is resistant to such thiocarbonyl-containing antituberculosis medications, as opposed to those frameshifts or polymorphisms that result in drug sensitivity. The post filing date art teaches that the "extensive cross-resistance among these compounds predicts multiple overlapping mechanisms of resistance among clinically used antituberculars: target-associated between ETA, thiacetazone, and thiocarlide." The reference makes the conclusion that "such considerations complicate appropriate drug treatment(PNAS, 2000)." Thereby, the scope of the claims do not bear a reasonable correlation to the scope of enablement provided by the specification and undue experimentation would be required to practice the full scope of the claims because this would require randomized searching of mutations in the entire EtaA gene that would cause an oxidation deficiency. While the specification provides results regarding the presence of mutations listed in the table on page 5 of this office action, the specification has not taught an association between these mutations and the actual effect they have on the bacterium's ability to oxidize and therefore on its potential for resistance. Such random trial by error experimentation is considered to be

undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

Therefore, the specification does not provide the guidance necessary to distinguish between mutations that are associated with oxidative capabilities and mutations or polymorphisms that are not associated with conferring either resistance or sensitivity to drugs as a result of their oxidative capacity. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 12 and 29 are both indefinite over the recitation of "wherein said known EtaA gene…is selected from the group consisting of" and "wherein said mutated EtaA gene…ditto" respectively because the recited group consists of mutations and polymorphisms and not genes. The claims should be amended to clarify that the known EtaA gene comprises a mutation or polymorphism selected from the group consisting of…etc.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Boehringer-Mannheim 1997 Biochemicals catalog.

The catalog teaches a product consisting of a container filled with a mixture of hexamer nucleotides of all possible sequences for random-primed DNA labeling which could be used as primers for amplifying an EtaA gene. It is noted that the claim does not require that the primers specifically amplify the EtaA gene, but only require that primers are capable of amplifying the EtaA gene

Furthermore, as stated in MPEP 211.02, "When the claim is directed to a product, the preamble is generally nonlimiting if the body of the claim is directed to an old composition and the preamble merely recites a property in the old composition. *Kropa v. Robie,* 187 F.2d at 152, 88 USPQ at 480-481". The MPEP (2112) further states that the "claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable". Accordingly, the identification of a new use (i.e. of determining the ability of a *Mycobacterium tuberculosis* bacterium to oxidize a thioamide) for the known kit comprising primers for amplfifying an EtaA gene located in a container does not render the kit novel.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Badcock et al in view of Philipp et al and in further view of Ahern et al.

Badcock et al. teach the EtaA gene of *Mycobacterium tuberculosis* and its probable function as a monooxygenase(See CDS nt position 14983..16452 of Accession # Z83864)

Badcock et al. do not teach a kit containing primers to amplify an EtaA gene.

However, Philipp et al. teach an integrated map of the genome of the tubercle bacillus, *Mycobacterium tuberculosis* H37Rv, and comparison with *Mycobacterium leprae.* The reference further teaches that the "goal of such a study was to elucidate the genomic organization of *Mycobacterium tuberculosis* and to establish a set of ordered DNA fragments, a valuable genetic resource"(Philipp, Pg. 3137). The reference further teaches that "several recent examples leading to the identification of genes involved in drug resistance or encoding new therapeutic targets testify to the power of the approach." Furthermore, the reference teaches the use of PCR amplification using primers specific to the *Mycobacterium tuberculosis* sequence of genomic DNA in order to facilitate gene mapping , data handling and analysis(Pg. 3133).

However, Ahern et al. teaches the use of kits in "some tasks such as constructing genomic libraries, designing primer sets, or synthesizing nucleic acids"(The Scientist, 1995), for the expected benefit of buying premade reagents and kits are convenient and they save time.

Therefore it would have been obvious to one skilled in the art at the time the invention was made to use the kit concept of Ahern et al, to have encompassed the EtaA gene sequence and motivation provided by Philipp et al. and monooxygenase function as provided by Badcock et al. to make a kit containing primers for amplifying an EtaA gene of *Mycobacterium tuberculosis* bacterium.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantai Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

November 18, 2002

CARLA J. MYERS
PRIMARY EXAMINER